

**REMARKS**

Reconsideration is requested.

Claims 5-10 and 13 are pending. Claims 1-4, 11, 12 and 14-36 have been canceled, without prejudice.

The PTO IFW contains a copy of an International Examination Report on Patentability dated July 22, 2005 issued in connection with PCT/EP2004/000408 which lists the following documents: WO 00/31548, WO 02/09761, and Brummelkamp et al, "Loss of the cylindromatosis tumour suppressor inhibits apoptosis by activating NF-KB", NATURE, August 14, 2003, Vol. 424, pp 797-801. The PTO IFW also contains a copy of an International Search Report mailed January 25, 2005 in connection with PCT/EP2004/000408 which lists the following documents: Database Biosis 'Online!', Biosciences Information Service, 7 March 2001, Datta et al., A specific region in the beta domain of von Hippel-Lindau gene product is sufficient to inhibit both renal tumor cell proliferation and invasion, XP002296354, Abstract; Li et al., Ubiquitination of a Novel Deubiquitinating Enzyme Requires Direct Binding to von Hippel-Lindau Tumor Suppressor Protein, vol. 277, no. 7, February 15, 2002, pp. 4656-4662, XP002296282; and Tyers et al., VHL: A very hip ligase, vol. 96, no. 22, October 26, 1999, PNAS, pp. 12230-12232, XP002296283. Copies of all of the references have been supplied and are contained in the PTO IFW with a listing of each on a PTO 1449 Form, or equivalent. The Examiner has been requested to return a copy of the PTO 1449 Forms as acknowledgement of consideration of the references as well as the search reports.

The Examiner has acknowledged consideration of the cited art. See "List of References cited by applicant and considered by examiner" indexed in the PTO IFW on January 4, 2008, and "List of references cited by examiner" indexed in the PTO IFW on January 4, 2008.

The Examiner has lined-through the listing of the Search Reports on the PTO 1449 Forms even though the Examiner states on page 2 of the Office Action dated July 1, 2008 that Rule 1.98(a)(2) requires a legible copy of "(4) all other information, or that portion which caused it to be listed." The applicants submit that the Search Reports were properly listed on the previously-submitted PTO 1449 Forms and the Examiner's acknowledgement that the same have been considered is requested. Search Reports are regularly considered by U.S. Patent Examiners and listed on the face page of issued U.S. patents. The applicants note in this regard that a "Quick Search" of the on-line U.S. Patent Office database reveals that 80,737 U.S. patents have issued since 1976 wherein the phrase "Search Report" is contained in the "Other References" field on the first page of the patent. Return of an initialed copy of the previously-filed PTO 1449 Forms, pursuant to MPEP § 609, as an acknowledgement of the Examiner's consideration of the previously-filed Search Reports is requested.

The Office Action of July 1, 2008 further states that "the references cited in the Search Report have not been considered." See page 2 of the Office Action. Clarification is requested as initialed copies of the PTO 1449 forms listing the references have been received from the Examiner and are contained in the PTO IFW.

Claims 10 and 13 have been revised, without prejudice, to advance prosecution. No new matter has been added. Support for the revision to claim 10 may be found, for example, on pages 19 and 41 of the specification. Support for the revision to claims 13 may be found, for example, in the paragraph spanning lines 4 to 14 on page 2 of the application and page 21, lines 25-26. No new matter has been added.

The Section 112, first paragraph "written description", rejection of claims 10 and 13 is obviated by the above amendments. Entry of the present Amendment is requested therefore to at least reduce this issue for appeal. Entry of the present Amendment and withdrawal of the rejection are requested.

The Section 103 rejection of claims 5-9 over Li et al (BBRC, Vol. 294, pp 700-709, 2002) and Li et al (JBC, Vol. 277, No. 7, pp 4656-4662, 2002) and Jones (FASEB Journal, Vol. 16, pp 264-266, 2002) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

Li et al (JBC) is understood by the applicants to describe the discovery of VDU1. This protein is found (a) to interact with pVHL [page 4657, col. 1]; (b) to have de-ubiquitinating activity [paragraph bridging pages 4659-4660]; and (c) to be itself ubiquitinated for degradation [page 4657, col. 1].

This citation also states that pVHL binds to HIF, targeting it for ubiquitination [page 4662, col. 1] and that pVHL binds to VDU1 targeting it for ubiquitination.

Although a number of possibilities are put forward in this citation, there is no clear suggestion or indication that VDU1 acts primarily as a de-ubiquitinating enzyme, or what the potential substrates may be for that de-ubiquitinating activity. To the contrary, Li et

al (JBC) concentrates on the correlation between ubiquitination and degradation. Thus, just as pVHL binds to HIF, targeting it for ubiquitination and degradation, so does pVHL bind to VDU1, also targeting it for ubiquitination and thus degradation.

While VDU1 may be shown to have deubiquitinating activity, this is demonstrated using a synthetic substrate Ub-GST. There is no suggestion that VDU1 targets HIF- $\alpha$  for de-ubiquitination.

The applicants understand Li et al (BBRC) to concentrate on the discovery of VDU2 and determine that this, just like VDU1 and HIF- $\alpha$ , are targeted by pVHL for ubiquitination and degradation. In the discussion of this article, on page 708, Li et al suggest that pVHL may down-regulate the deubiquitinating pathways controlled by VDU1 and VDU2 – however, there is no teaching or suggestion in either this article or any of the other citations provided by the Examiner of any pathway controlled by VDU1 or VDU2 or of any substrate for de-ubiquitination by VDU1 or VDU2.

The last paragraph of Li et al (BBRC) asks numerous questions, such as the following:

Can VDU1 and VDU2 deubiquitinate the ubiquitinated downstream targets of pVHL-E3 ligase, such as HIF- $\alpha$ ?

Can VDU1 or VDU2 deubiquitinate the ubiquitinated pVHL to salvage it from degradation?

Is VDU1 or VDU2 over-accumulated in VHL-related tumours?

However, there is no indication of whether pVHL mediated ubiquitination of HIF- $\alpha$  occurs in vivo before or after ubiquitination by pVHL of VDU1 or VDU2. As both of the

Li articles propose that ubiquitination targets the compound for degradation, the ordinarily skilled person would not have been able to determine from the Li citations whether HIF- $\alpha$  is actually degraded before VDU1 and VDU2 are ubiquitinated. Furthermore, if ubiquitination of VDU1 and VDU2 leads to their degradation, as is proposed by both the Li articles, it is not predictable from the cited art at what stage these enzymes exert their de-ubiquitinating activity.

Thus, contrary to the Examiner's suggestion, the applicants submit that none of the cited art either teaches or suggests the specific steps of the claimed invention, i.e. the bringing together of a potential modulator, VDU1 and a ubiquitinated VDU1 substrate to determine the ability of the modulator to modulate the stabilisation and/or state of ubiquitination of the substrate, followed by bringing together that modulator, VDU1 and HIF- $\alpha$  and determining the effect of the modulator on the stability or state of ubiquitination of HIF- $\alpha$ . The cited Jones reference is not believed to cure the above-noted deficiencies of the cited Li et al references.

The claims are submitted to be patentable of the cited combination of art and withdrawal of the Section 103 rejection based on same is requested.

Entry of the present Amendment and a Notice of Allowance are requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required in this regard.

BERNARDS et al.  
Appl. No. 10/542,024  
Atty. Ref.: 620-378  
Amendment After Final Rejection  
Tuesday, September 2, 2008

Respectfully submitted,

**NIXON & VANDERHYTE P.C.**

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